Individual dynamic predictions in joint analysis for nonlinear marker evolution and competing risk data: application on patients admitted in Intensive Care Unit for sepsis

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Background: Joint models of longitudinal process and time to event data have recently gained attention specially for providing individualized dynamic predictions. In the presence of competing risks, such predictions are only available from joint models involving linear or generalized linear mixed-effects model for the longitudinal part [1,2]. Here we propose to extend the modelling to full parametric nonlinear mixed-effects models in order to provide dynamic predictions of the future longitudinal evolution and the associated risk of event of interest. We applied this approach on patients admitted in Intensive Care Unit (ICU) for sepsis with daily SOFA score [3] assessments. The objective is to predict dynamically and jointly the future patients SOFA evolution with 30-day risk of death.

Methods: A subset of OUTCOMEREA database including 6046 patients with sepsis or septic shock admitted in French ICUs between 1995 and 2015 is considered for the analysis. We combined a parametric nonlinear mixed-effects submodel to model the SOFA evolution and parametric subdistribution hazards submodels adjusted on age, to model the risk of death in the presence of ICU discharge as a competing event. The nonlinear structural function allows monotone as well as non-monotone SOFA trends. Parameters are estimated on the training data set composed of 4050 random patients of the data set by the maximization of the likelihood using the SAEM [4] algorithm implemented on Monolix software. Using Metropolis-Hastings [5] algorithm implemented in Monolix and the estimated population parameters, the *a posteriori* distribution of the individual parameters is computed for a new patient knowing his SOFA measurements until a given landmark time. Four landmark times are considered for the analysis at 1, 5, 10 and 15 days after patient admission. Performances are assessed with time dependent Area Under the Curve (AUC) and Brier score [6] on an external validation set, composed of the remaining 1996 patients of the data.

Results: Median age was 65.1 years (IQR: 52.7 – 76.2) and median admission SOFA was 6 (IQR : 4 – 9). 19% of the patients died 30 days after their admission while 72% were discharged. As expected, an increase in SOFA score is significantly associated with an increase of the death risk and a decrease of the discharge risk. The joint modelling approach leads to good predictive performances for the earliest landmark time: a 1-day follow-up leads to an AUC of 0.72 (with 95% CI: [0.69,0.75]) and a Brier score of 0.15 (with 95% CI: [0.14,0.16]). Later landmark times are associated with very good predictive performances: for landmark =15d, AUC = 0.90 (with 95% CI: [0.88,0.92]) and Brier score = 0.10 with 95% CI: [0.09,0.11]).

Conclusion: The joint modelling approach allows to quantify the future risk of death associated with any individual SOFA history while genuinely overcoming known issues relative to time-dependent covariates in subdistribution hazards models. In fact, the joint analysis considers the endogenous nature of the covariate, his complete history and his measurement error. The proposed model

applied for individual dynamic predictions can be useful for clinicians in routine medical practice, as the identification of most at risk patients as early as possible, and support clinical decisions such as therapeutic escalation or limitation. The methodology can be easily applied to other fields when a marker is associated with the occurrences of multiple events.

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